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ORIGINAL REPORT

Prophylactic Oophorectomy Reduces Breast Cancer Penetrance During Prospective, Long-Term Follow-Up of *BRCA1* Mutation Carriers

Joan L. Kramer, Isela A. Velazquez, Bingshu E. Chen, Philip S. Rosenberg, Jeffery P. Struewing, and Mark H. Greene

From the Clinical Genetics and Biostatistics Branches, Division of Cancer Epidemiology and Genetics, and Laboratory of Population Genetics, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD.

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Address reprint requests to Joan L. Kramer, MD, Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, Room 7016, MSC 7231, Rockville, MD 20852; e-mail: kramerj@mail.nih.gov.

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ABSTRACT

Purpose
Breast cancer penetrance estimates in *BRCA1* mutation carriers have varied from 40% to 85%; this heterogeneity has been attributed to variations in risk among different study populations. No study has taken oophorectomy status into account in estimating penetrance. Because prophylactic oophorectomy reduces breast cancer risk by approximately 50%, we hypothesized that population differences in oophorectomy prevalence might significantly influence breast cancer penetrance estimates.

Methods
Females from multiple-case breast/ovarian cancer families that segregate deleterious *BRCA1* mutations were observed prospectively for breast cancer incidence and oophorectomy.

Results
Within this cohort, 33 cases of breast cancer developed in 98 women with deleterious *BRCA1* mutations during follow-up, yielding an estimated cumulative lifetime breast cancer risk of 80%. This estimate increased to 94% when the study participants were censored at the time of oophorectomy. Six of the 33 mutation-positive women who underwent oophorectomy during follow-up developed breast cancer, compared with 27 of 65 mutation carriers with intact ovaries (hazard ratio = 0.38; 95% CI, 0.15 to 0.97). Estimates of absolute breast cancer risk demonstrated that the protective effect of oophorectomy was strongest among women who were premenopausal at the time of surgery. When surgical status was ignored, the strong protective effect of oophorectomy, coupled with the high prevalence of the procedure in these families, led to a significantly lower estimate of the breast cancer penetrance in *BRCA1* mutation carriers.

Conclusion
Differing rates of oophorectomy likely represent an underappreciated basis for a portion of the heterogeneity in estimated breast cancer penetrance described in *BRCA* mutation carriers, particularly mutation carriers from extensively affected, multiple-case families.

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INTRODUCTION

Bilateral oophorectomy was introduced as a risk-reducing procedure in hereditary breast/ovarian cancer (HBOC) families long before the discovery of the *BRCA1* and *BRCA2* genes. Although the primary aim of this procedure was to reduce the risk of ovarian cancer, more recent studies have suggested a favorable effect of oophorectomy on the risk of breast cancer. Small, largely retrospective cohort studies have demonstrated that the postoophorectomy incidence of breast cancer among *BRCA* mutation carriers is substantially lower than the incidence seen in mutation carriers with intact ovaries, with hazard ratios (HR) ranging from 0.32 to 0.53.[1-3]

Despite the apparent strength of this association, the relationship between oophorectomy status and breast cancer risk has not been taken into account in previous analyses aimed at quantifying the age-specific penetrance of breast cancer in *BRCA* mutation carriers. Published estimates of breast penetrance in *BRCA1* carriers are notably heterogeneous, with results based on high-risk families ranging from 50% to 85% (Table 1).[4-17] Explanations for this variability have included genuine differences in risk between different populations, differences in study setting/design, allelic heterogeneity, differences in modifying factors, and chance.[18-20] However, when considering modifying factors that might influence penetrance estimates observed in different studies, little attention has been paid to the rate of bilateral oophorectomy in these study populations. In our analysis of prospective cancer incidence after family ascertainment in *BRCA1* mutation–positive families, the strong influence of oophorectomy became apparent.

METHODS

Study Population

Study participants included 673 females from 23 self-referred and physician-referred HBOC families participating in ongoing Institutional Review Board–approved studies at the National Cancer Institute. Our program currently has a cohort of 60 HBOC families under active follow-up. Previous publications have detailed the clinical features and genetic evaluation of this cohort.[21-26] This analysis was confined to the 23 families from the cohort that have been found to carry a deleterious mutation in *BRCA1*. Small numbers of participants precluded including the *BRCA2* families in our cohort in this analysis. Families with variants of uncertain significance were excluded from the analysis. The *BRCA1*-positive families were characterized by multiple cases of breast and/or ovarian cancer before enrolling onto our registry, with a mean of 2.7 cases of breast cancer and 3.0 cases of ovarian cancer per family diagnosed before ascertainment.

Table 1. Summary: Breast Cancer Penetrance Among *BRCA1* and *BRCA1/2* Mutation Carriers

Population	Reference	Cumulative Incidence of Breast Cancer (%)			
		BRCA1		*BRCA1/2*	
		50 Years	70 Years	50 Years	70 Years
Linkage analysis, maximization of logarithm of the odds score					
33 *BRCA1*-linked families, BCLC	Easton et al[4]	51	85		
237 HBOC families, BCLC	Ford et al[5]	49	71		
Incidence of second cancers after breast cancer					
33 *BRCA1*-linked families, BCLC	Easton et al[4]	50	65		
Analysis of family members of:					
Jewish women with ovarian cancer	Levy-Lahad et al[6]	30*	50*		
Jewish HBOC families	Levy-Lahad et al[6]	37*	64*		
Modified segregation analysis, all available relatives tested (MENDEL†)					
Australia, breast cancer age < 40 years	Hopper et al[7]			10	40
Kin cohort					
Community-based Washington-area Jews	Struewing et al[8]	38	59	33	56
Jewish women with breast cancer	Warner et al[9]		60		
Jewish women with ovarian cancer	Moslehi et al[10]	31‡	44§		
Unselected patients with ovarian cancer	Risch et al[11]		68‖		
Modified segregation analysis (MENDEL†)					
Breast cancer patients, age < 55 years	Anglian Breast Cancer Study Group[12]	32	47	21	54
Families with 2+ patients with ovarian cancer	Antoniou et al[13]	39	72		
Unselected patients with ovarian cancer	Antoniou et al[13]	34	50		
Unselected ovarian and breast cancers, 22 studies	Antoniou et al[14]	38	65		
Australian multiple-patient families	Scott et al[15]		48		
Relative risk times population rates					
Jewish hospital-based ovarian cancers	Satagopan et al[16]	18	59		
Direct Kaplan-Meler estimates restricted to relatives known to be mutation positive					
Unselected Jewish breast cancers (NYC)	King et al[17]	39	69		

NOTE. Table 1 modified from the National Cancer Institute's Genetics of Breast and Ovarian Cancer (PDQ) at http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/healthprofessional, as of January 31, 2005.
Abbreviations: BCLC, Breast Cancer Linkage Consortium; HBOC, hereditary breast/ovarian cancer; NYC, New York City.
*Outcome is breast or ovarian cancer.
†MENDEL 5.7 (University of California Los Angeles Software Distribution; Los Angeles, CA).
‡Incidence to age 55 years.
§Incidence to age 75 years.
‖Incidence to age 80 years.

Data Collection

Information regarding families in this cohort has been collected systematically since 1969, when the first family was ascertained. Data were obtained through demographic, medical history, cancer risk factor, and family history questionnaires completed by family members at the time of enrollment. This information has been updated periodically, both by passive reporting from family informants and through active follow-up by study investigators. Reported cancers were objectively confirmed through the collection of death certificates, medical records, pathology reports, and central review of surgical pathology slides at the National Institutes of Health. In preparation for the current analysis, individual research records and computerized data files were systematically reviewed by the study investigators. Special attention was paid to documenting all surgical procedures (eg, mastectomy and oophorectomy) that would result in the removal of any of the target organs of interest, and to distinguishing between primary cancers and metastatic disease. All study participants provided written informed consent, both for general protocol participation and for research-based or clinical germline mutation testing.

Study Design

The 673 individuals were drawn from the 23 *BRCA1*-positive families for the present analysis based on the following eligibility criteria: female sex; bloodline family member; no history of breast cancer before ascertainment; no history of bilateral mastectomy; and age $\geq$ 20 years by the study closing date (June 30, 2003). A diagnosis of malignancy other than breast cancer did not affect eligibility for this analysis. The incidence of breast cancer among study participants was calculated from the date of family ascertainment. The 63 patients with breast cancer who had been diagnosed before family ascertainment were excluded from this analysis. For the analysis of the effect of oophorectomy, all individuals who had undergone the procedure were included, without regard to the indication for the procedure.

Mutation Testing

Various methods were used to screen for mutations in the families in this cohort, with results confirmed by direct sequencing. Ultimately, affected individuals from all families negative by our screening methods were fully sequenced by Myriad Genetics Laboratories, Inc (Salt Lake City, UT). In addition, all families with no mutation detected by sequencing were studied (by Myriad Genetics Laboratories, Inc) for the presence of large germline deletions in *BRCA1*.[27] After a deleterious mutation was identified in a kindred, individual family members were offered clinical mutation testing for the previously n = n identified family mutation. Multiple individual mailings and cohort-wide distribution of study-related newsletters have been used to bring the availability of genetic testing to the attention of all cohort members for whom we had a current mailing address. For our analysis, mutation status was assigned based on either direct testing or direct inference (based on a participant's relationship to an individual with known mutation status). Mutation status was not assigned probabilistically. The participants for whom mutation status could not be determined with certainty (ie, with neither an informative relative nor a source of DNA available for testing) remained as a separate group with the designation of mutation unknown. Of the 673 women in our analysis, a total of 98 were designated as *BRCA1* mutation positive (of these women, 15 were inferred positive based on having a child who was found to carry the family mutation). In addition, a total of 353 women were determined to be mutation negative, 106 of whom were inferred negative based on having a parent that tested negative for the family mutation. Mutation status could not be determined in 222 women, the majority of whom simply declined genetic testing.

Statistical Methods

Actuarial analysis. The cumulative, age-specific probabilities of developing breast cancer were estimated in carriers and noncarriers of *BRCA1* mutations using the Kaplan-Meier (KM) product-limit method, with age as the time variable, modified to account for late entry.[28] Person-years of observation (PYO) accumulated from the date of family ascertainment by the National Cancer Institute or the participant's 20th birthday, whichever was later, until the participant developed breast cancer or had a censoring event. Censoring occurred as a result of bilateral mastectomy, death, or the study closing date (June 30, 2003).

Effect of oophorectomy. To assess the impact of oophorectomy on the estimated penetrance of breast cancer, the KM analysis was repeated with the addition of oophorectomy as a censoring event. This allows participants undergoing oophorectomy to contribute any PYO before the procedure to the "no oophorectomy" group. A Cox proportional hazards model incorporating oophorectomy as a time-dependent covariate was used to estimate the effect of oophorectomy on the incidence of breast cancer in *BRCA1* mutation carriers. To provide estimates of the absolute risk of breast cancer by age in mutation carriers, landmark analyses were performed in which oophorectomy was treated as a time-fixed covariate, as defined at the beginning of a given age interval. Follow-up time was divided into 10-year intervals, with mutation carriers divided into two groups based on oophorectomy status at the beginning of that interval (and conditional on the participant being alive and breast cancer free at that time). A competing risks model (with death as the competing risk) was then used to estimate the 10-year cumulative incidence of breast cancer in the two groups of *BRCA1* mutation carriers (ie, those with and without ovaries).

RESULTS

Six hundred seventy-three eligible women were observed prospectively for a mean of 16.5 years, accumulating 11,105 PYO. Of these women, 98 were *BRCA1* mutation positive, and 353 were mutation negative; mutation status could not be determined in 222 women. Thirty-three *BRCA1*-positive women developed breast cancer during prospective follow-up, whereas only five *BRCA1*-negative women developed breast cancer (Table 2). The KM estimates of the risk of breast cancer among *BRCA1*-positive women at ages 50 and 70 years were 0.44 (SE = 0.07) and 0.76 (SE = 0.08), respectively, with the lifetime KM risk estimated at 0.80 (SE = 0.07). In contrast, the KM lifetime risk of breast cancer among mutation-negative women was 0.068 (SE = 0.033; Table 3).

Among the 98 mutation-positive participants, 33 women underwent oophorectomy, and 65 women retained their ovaries. Breast cancer occurred in six participants 1 to 16 years after the procedure during 284 PYO

Table 2. Descriptive Sample Characteristics

BRCA1 Mutation Carrier Status	No. of Patients	PYO	Mean Follow-Up per Patient (years)	Patients With Breast Cancer	Age at Diagnosis (years)	
					Mean	Range
Positive	98	1,382	14.1	33	46.7	26-77
Oophorectomy	33	284*	8.6	6	47.4	
Negative	353	6,209	17.6	5	53.3	42-68
Oophorectomy	34	646*	19	1	50	
Unknown	222	3,513	15.8	5	45.4	28-71
Oophorectomy	18	222*	12.3	0	NA	
All	673	11,105	16.5	43	47.3	26-77

Abbreviations: PYO, person-years of observation; NA, not applicable.
*Observation from date of oophorectomy until breast cancer or censoring event (PYO accumulated before oophorectomy were allocated to the no oophorectomy group). In the mutation-positive group, the hazard ratio for breast cancer was 0.38 among women who had undergone oophorectomy compared with women whose ovaries were intact.

in the oophorectomy group, whereas breast cancer occurred in 27 participants during 1,098 PYO among women with intact ovaries (HR = 0.38; 95% CI, 0.15 to 0.97; Table 2). Recalculating the KM actuarial analysis with oophorectomy included as a censoring event resulted in an increase of 18% in the estimate of the lifetime risk of breast cancer in *BRCA1* mutation carriers (lifetime risk: 0.94; 95% CI, 0.82 to 1.0). Combining this penetrance estimate (0.94) with the HR associated with oophorectomy (0.38) allowed us to calculate a crude lifetime breast cancer penetrance estimate of 36% in the subset of women who had undergone oophorectomy.

It is invalid to use the standard actuarial method (KM) to estimate age-specific risks of breast cancer in the oophorectomy group because it treats oophorectomy (performed at any age) as a baseline factor.[29] Thus, we used an alternate analytic strategy to estimate the absolute risk of breast cancer after oophorectomy at various ages. Landmark analysis, which allows oophorectomy to be treated as a time-fixed covariate at specific ages, was performed using the competing risk model to estimate the absolute risk of breast cancer over 10-year intervals for women with and without ovaries. These analyses suggest that a 40-year-old mutation carrier who is breast cancer free and with intact ovaries has a 10-year breast cancer risk of 0.32 (SE = 0.13) compared with 0.11 (SE = 0.10) for a female carrier of the same age who had undergone oophorectomy. Among 50-year-old mutation carriers, the corresponding risks in the subsequent 10 years were 0.28 (SE = 0.14) and 0.19 (SE = 0.12), whereas, for 60-year-old mutation carriers, the values were 0.25 (SE = 0.18) and 0.14 (SE = 0.13), respectively. The reduction in the absolute risk of breast cancer among women who underwent oophorectomy was most prominent when the surgery was performed at younger ages (ie, < 40 years; Fig 1).

Table 3. Actuarial Risk of Breast Cancer by Age

Age (years)	Cumulative Risk (Kaplan-Meier) of Breast Cancer					
	BRCA1 Positive				*BRCA1* Negative	
	Overall		With Ovaries*			
	Mean	SE	Mean	SE	Mean	SE
50	0.44	0.07	0.49	0.09	0.017	0.012
70	0.76	0.08	0.92	0.08	0.068	0.033
80	0.80	0.07	0.94	0.06	0.068	0.033

*In this analysis, oophorectomy was a censoring event.

DISCUSSION

We prospectively evaluated the risk of breast cancer in 98 women with, and 353 women without, germline *BRCA1* mutations from extensively affected, multiple-case families, all of whom were under long-term follow-up. Because one third of the mutation carriers had undergone risk-reducing oophorectomy (RRO), we were able to examine the impact

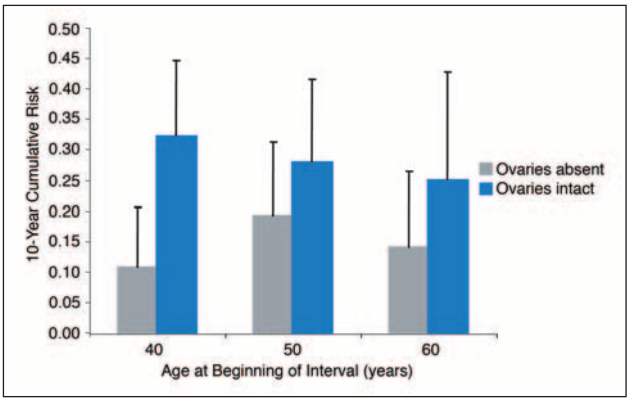

Fig 1. Absolute risks of breast cancer by age and oophorectomy status. Error bars indicate the SE corresponding to each point estimate. The hazard ratio for breast cancer was 0.38 (P = .043) among women without ovaries compared with women whose ovaries were intact.

of oophorectomy on breast cancer penetrance. Among *BRCA1* mutation carriers, oophorectomy was associated with a 62% (95% CI, 3% to 85%) reduction in breast cancer risk. This reduction in risk, coupled with the high prevalence of oophorectomy in this cohort, yielded a significantly lower observed breast cancer penetrance (lifetime penetrance = 80%) in the total mutation-positive cohort than what would have been observed had there been fewer (or zero) RRO procedures. Penetrance was higher among carriers with intact ovaries in the actuarial analysis; adding oophorectomy to the list of censoring events increased the estimated lifetime risk of breast cancer in the entire cohort to 94%.

Our program has had a long-standing interest in familial ovarian cancer[21]; many of these families were ascertained because they had multiple family members with ovarian cancer. In addition, we were among the earliest advocates of RRO as a management strategy in high-risk women.[22] Many family members underwent RRO based on family history and perceived risk of ovarian cancer, before germline mutation testing to establish carrier status was available. Because the families reported here have been under prospective follow-up for up to 35 years and because they are likely to have unusually high rates of RRO, our cohort is particularly well suited to exploring the interaction between breast cancer penetrance and oophorectomy status.

A number of previously n = n published studies have provided estimates of breast cancer penetrance in carriers of *BRCA* mutations. Although population-based studies have generally resulted in lower breast cancer penetrance estimates than studies of carriers from multiple-case families, considerable variability in these estimates remains, even among studies targeting similar populations (eg, high-risk, multiple-case families; Table 1). Our initial breast cancer penetrance estimates (76% at age 70 years, with a lifetime penetrance of 80%) are consistent with other studies of multiple-case families.[30,31] Our analysis revealed no evidence of a birth cohort effect (data not shown).

Because data regarding the incidence of oophorectomy in other cohorts used to estimate breast cancer penetrance have not been reported, we cannot compare the incidence in our study population to that of similar studies.[4,17,32] Nonetheless, other data indicate that 41% to 58% of selected mutation carriers are opting to have their ovaries removed,[3,33] suggesting that the interaction between RRO and breast cancer risk is likely to be substantial in contemporary high-risk cohorts.

The breast cancer risk reduction associated with oophorectomy in this study is consistent with other such estimates in the literature. A prospective study demonstrated a 59% decreased contralateral breast cancer risk after oophorectomy in *BRCA* mutation carriers (HR = 0.41; 95% CI, 0.18 to 0.90).[34] A largely retrospective analysis reported a 50% reduction in breast cancer risk among oophorectomized mutation carriers versus carriers with intact ovaries.[2]

In an ongoing prospective study of oophorectomy and cancer risk in Ashkenazi Jewish *BRCA* mutation carriers, RRO was associated with a 68% decreased risk of breast cancer (HR = 0.32; 95% CI, 0.08 to 1.20). This study was hampered by a relatively short follow-up period (mean follow-up, 23 months for the breast cancer outcome), and this finding did not reach statistical significance.[3] In contrast, our cohort contained fewer mutation carriers than this study (98 *v* 170 carriers, respectively), but it did not exclude 353 mutation-negative participants, and the participants were under observation for a much longer period (mean follow-up, 16 years).

To what extent do our penetrance estimates apply to *BRCA1* mutation carriers in general? We believe they apply most reliably to *BRCA1* mutation carriers from families with ascertainment criteria similar to ours. Our families presented with an average of 2.7 breast cancers and 3.0 ovarian cancers at ascertainment, all of which we excluded from the present analysis. If the high incidence of cancer that brought the family to our attention initially was a result of random variation or time-limited factors, we would have expected the prospective cancer incidence to have been lower than it was.[35] The persistent, high prospective incidence of breast cancer is particularly noteworthy, considering that one third of our participants underwent RRO, which is a procedure that would be expected to reduce their breast cancer incidence.

The observation that the protective benefit related to oophorectomy was largest in women who were premenopausal at the time of surgery is compatible with the hypothesis that loss of ovarian estrogen mediates the reduction in breast cancer risk. Although the effect of oophorectomy is easiest to appreciate in a cohort of high-risk families such as ours, the risk reduction associated with surgery might be expected to apply to lower risk populations as well. In fact, this same phenomenon has been reported in the general population, in which surgical menopause is associated with a reduction in breast cancer risk.[36-39] A protective effect of oophorectomy was also recently reported in intermediate-risk women.[40] Nonetheless, the incidence of RRO is likely to be low in population-based cohorts, so our findings cannot account for the penetrance differences that have been observed between high-risk cohorts and those derived from the general population.

An additional methodologic strength to our study is the derivation of estimates of absolute risk of breast cancer, by age, among mutation carriers with and without intact ovaries. Prior studies aimed at quantifying breast cancer risk reduction in this setting have computed HRs, which is a measure of relative risk. Our study is the first analysis to derive absolute risks, which is information that is particularly valuable when counseling women who are contemplating risk-reducing surgery because patient comprehension of risk seems to be enhanced when absolute rather

than relative comparisons are offered.[41,42] Thus, for example, we can now inform a 40-year-old mutation carrier with intact ovaries that her risk of breast cancer over the subsequent 10 years is approximately 32% (or one chance in three) compared with 11% (one chance in 10) among similarly aged women who have undergone oophorectomy. This information conveys the magnitude of the potential risk reduction after bilateral oophorectomy in terms that are readily understood. Our data also support the expectation that the oophorectomy-related reduction in breast cancer risk is greatest among women who are young (premenopausal) at the time of surgery, thus providing useful information regarding the timing of surgical intervention in high-risk women.

Finally, the lifetime risk of breast cancer among the mutation-negative women in this cohort was 6.8%, which is an estimate similar to that expected in a general population setting. This observation supports the current practice of counseling mutation-negative women that their risk of breast cancer is similar to that of similarly n = n aged, unselected women.

One important limitation of our study is the relatively small number of known mutation carriers, but this constraint is offset, at least in part, by the unusually prolonged follow-up (up to 35 years) and the large number of informative, known mutation-negative participants. The PYO from our mutation-positive cohort (1,382 PYO) is more than twice the PYO reported in other recently n = n published prospective studies of breast cancer risk in *BRCA* carriers.[3,33,43,44] Still, although a purely prospective study design helps to minimize potential ascertainment bias, this design required the (appropriate) exclusion of the 63 breast cancers that had occurred before ascertainment.

In addition, there is some potential for bias in breast cancer penetrance estimates as a consequence of the large number of participants with unknown mutation status. If the decision to undergo mutation testing was influenced by the history of cancer in a given participant and her immediate family, the group of participants with unknown mutation status might not be a random subset of the overall study cohort. In particular, if untested participants were preferentially derived from branches of the family that are cancer free, then the penetrance estimates would be biased downward. However, if this group contained a substantial number of mutation carriers who remained cancer free, our penetrance estimates for carriers would have been biased upward. The observation of moderate excesses of *BRCA*-related cancers in the mutation-unknown group (data not shown) implies that there are a significant number of unidentified mutation carriers in this family subset and argues against both bias scenarios.

Finally, many individuals opted for oophorectomy based on perceived risk of ovarian cancer before the availability of genetic testing for *BRCA1* mutation. If families with a high incidence of ovarian cancer before ascertainment had inherently lower risks of breast cancer than the rest of the cohort, confounding by indication could have led to an overestimation of the risk reduction associated with oophorectomy.[45] We have no data to support such a hypothesis.

In conclusion, studies regarding the risk of breast cancer in carriers of *BRCA1* mutations began 10 years ago. Although oophorectomy has been gaining popularity as a means of reducing the risk of both ovarian and breast cancer in HBOC families,[3] quantitative studies of the lifetime breast cancer risk have ignored that surgical variable. Rather, studies of the risk-reducing effects of oophorectomy have been examined separately in matched cohort designs. The current study highlights the important relationship between estimates of breast cancer penetrance and the risk-reducing effect of oophorectomy. The recognition of oophorectomy as a breast cancer risk modifier suggests that it will be essential for future studies to define the incidence of oophorectomy in target cohorts and to incorporate this variable into quantitative analyses, because RRO seems to represent an underappreciated source of the heterogeneity in the estimates of breast cancer penetrance among carriers of *BRCA* mutations, particularly in the setting of multiple-case, high-risk families.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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